REMARKS

Claims 1-22 are currently pending in the instant application. In the Amendment, Applicants have requested that Claims 1-10, 21, and 22 be cancelled without prejudice. After entry of the Amendment, Claims 11-20 are pending in this application. Applicants request reconsideration of the objections and rejections as stated in the Office Action dated February 11, 2004, based on the foregoing amendments and the following remarks.

Specification and Priority

In the Office Action, the Examiner objected to the Specification for lacking appropriate subtitles with respect to different parts of the Specification. Further, the Examiner objected to the Specification for failing to include a reference to a French priority application. In response, Applicants request entry of the substitute Specification submitted herewith. The substitute Specification includes appropriate subtitles for each section of the Specification and a reference to the French priority application as required by the Examiner. Applicants contend that the substitute Specification contains no material that would qualify as new matter. Applicants have included a marked-up version of the substitute Specification showing changes made for reference.

Information Disclosure Statement

In the Office Action, dated February 11, 2004, the Examiner indicated that the Information Disclosure Statement ("IDS") filed July 10, 2003 fails to comply with 37 C.F.R. 1.98(a)(2) because it did not include copies of the references listed on the PTO Form SB/08. Applicants believe that copies of the references listed on the PTO Form SB/08 were included

with the IDS submitted on July 10, 2003. However, Applicants have enclosed herewith a supplemental IDS, PTO Form SB/08 dated May 11, 2003, additional copies of the references, and the required fee. Applicants respectfully request that the Examiner consider the references and initial the form PTO/SB/08.

Claim Rejections - 35 U.S.C. § 112, second paragraph

In the Office Action, dated February 11, 2004, the Examiner rejected Claims 11, 13, and 17 under 35 U.S.C. § 112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner stated that "[t]he term 'soft' in claims 11, 13, 17 is a relative term which renders the claim indefinite." Applicants respectfully traverse the rejection.

Applicants have enclosed herewith as attachments, pages 858-859 of the European Pharmacopoeia 3rd Edition (1997), and for English language reference, pages 1782-1783 from the British Pharmacopoeia 2001. The British Pharmacopoeia 2001 states that "Extracts comply with the requirements of the 3rd edition of the European Pharmacopoeia." (*See* British Pharmacopoeia, column 1, page 1, paragraph entitled "Extracts." These pharmacopoeias state:

> Soft extracts are preparations of an intermediate consistency, between liquid and dry extracts. They are obtained by partial evaporation of the solvent used for preparation. Only ethanol of suitable concentration or water is used. Soft extracts generally have a dry residue of not less than 70 per cent by mass. They may contain suitable anti-microbial preservatives.

(*See* European Pharmacopoeia column 1, page 859, paragraph entitled "Extraits mous ou fermes," and British Pharmacopeia, column 1, page 1783, paragraph entitled "Soft Extracts.") As such, Applicants contend that the meaning of the term "soft extract" was

known in the art and that one skilled in the art at the time the application was filed would understand the metes and bounds of the claims. Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Claim Rejections - 35 U.S.C. § 102

In the Office Action, dated February 11, 2004, the Examiner rejected Claims 11-13 and 15-17 under 35 U.S.C. § 102(b) as being anticipated by Franz *et al.* (U.S. 4,411,882). The Examiner asserted:

> Franz teaches methods of producing coated pellets that meet limitations of the instant process. Franz teaches pellets having the ranges of 0.5-1.25 mm in diameter which is well within the instantly claimed ranges of particle size. Franz's core contains a polymeric substance such as PVP. Franz then coates [sic] the pellets with a layer of coating containing ergot alkaloid which meets the limitation of the instant plant substance.

Applicants respectfully traverse the rejection for the reasons indicated below.

First, Franz *et al.* do not teach or suggest coating neutral particles with a layer that contains a plant substance. Ergot alkaloids are produced by the fungus *Claviceps purpurea*. *See* http://www.encyclopedia.com/html/e1/ergot.asp. Even though *Claviceps purpurea* may be found growing on a plant (*e.g.*, corn), ergot alkaloids are fungus substances not plant substances.

In addition, Franz *et al.* do not teach or suggest the coating of a neutral core. Rather, Franz *et al.* describe "galenical compositions" that include active cores. As stated by Franz *et al.*, "the term 'core' comprises any mixture of an ergot alkaloid and a sterol ether...that can be surrounded by a [sic] enteric-coating" (col. 1, lines 45-48 (emphasis added)). All of the examples disclosed by Franz *et al.* describe the preparation of compositions that include an

"active core." (*See* examples 1-5 and 14-17, which disclose compositions that include an ergot alkaloid as an active ingredient in the core). Franz *et al.* do not describe any compositions that include a "neutral core." Therefore, for the above-stated reasons, Applicants respectfully contend that Franz *et al.* do not anticipate the subject matter of the pending claims. Applicants request that the Examiner withdraw the rejection under 35 U.S.C. § 102(b) over Franz *et al.*

Claim Rejections - 35 U.S.C. § 103

In the Office Action, the Examiner also rejected Claims 11-20 under 35 U.S.C. § 103 as being unpatentable over Franz *et al.* Applicant respectfully traverse the rejection. As noted above, Franz *et al.* do not disclose "a layer containing a plant substance" as recited in the pending claims. Neither do Franz *et al.* disclose coating a "neutral core" as recited in the pending claims. Therefore, Franz *et al.* do not disclose all the limitations of the pending claims.

Further, Franz *et al.* do not suggest the limitations of the present claims. The problem intended to be solved by Franz *et al.* is the preparation of a galenic composition of ergot alkaloids, with prolonged effect, and with an improved bioavailability (col. 1, lines 7-10). Franz *et al.* attempt to solve this problem by applying an enteric coating onto an active core (col. 1, lines 28-35). In contrast, the present invention is not a prolonged release formulation. Rather, it relates to a process for preparing a reproducible, homogenous and stable formulation by coating a neutral core with a layer containing a plant substance. As such, one skilled in the art, in view of Franz *et al.*, would not be motivated to perform the processes

recited in the pending claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103 over Franz *et al.*

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 5/11/04

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Appl. Ser. No.: 09/312,485

MARKED UP VERSION SHOWING CHANGES MADE

U.S. PATENT APPLICATION

for

GRANULES CONTAINING A PLANT SUBSTANCE AND PROCESS FOR PREPARING THEM

Inventors: Patrice Debregeas
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GRANULES CONTAINING A PLANT SUBSTANCE AND PROCESS FOR PREPARING THEM

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims the benefit of French patent application FR 99 03075, filed March 12, 1999.

BACKGROUND

[0002] The subject of the present invention is a new formulation in the form of granules containing a plant substance as well as the process for preparing it.

[0003] More precisely, the present invention relates to granules containing at least one plant substance and each comprising a neutral core coated with a layer containing the said plant substance combined with a pharmaceutically acceptable excipient.

[0004] The formulations containing plant substances which are already described in the prior art are in the form of powders, granules, tablets or oral solutions.

[0005] The major problem with formulations in powdered form is that the plant powder has to be mixed with excipients which are also in powdered form. A mixture of powders is then obtained which is hardly homogeneous and reproducible.

[0006] Furthermore, powders are very hygroscopic and they therefore pump moisture from the granules and from the gelatin capsule, which become brittle. This poses problems of stability, and the proportion in the gelatin capsule is not homogeneous.

[0007] This problem is solved within the framework of the present invention because, in the case of the application of a plant substance in the form of a dry extract onto neutral micrograms, there is no mixing of powder but the application of the dry extract onto neutral granules with excipients which are not powders.

[0008] The granules according to the invention have the advantage of being easier to package into gelatin capsules than powders of being more stable to storage than the formulations of the prior art and of having a reproducible proportion.

[0009] As for tablets, they have the same problems as powders. Moreover, plant extracts are not always compressible and compressing agents are not always authorized in the food industry.

[0010] Finally, the oral fluid forms are often bitter and foul-smelling to the extent that sweeteners and stabilizers need to be added. In addition, the oral fluid forms may exhibit physical or chemical instability during storage, a low content of characteristic plant constituents, and frequently contain ethyl alcohol in a moderately large quantity, which is not generally desirable for the oral administration of medicinal products.

[0011] The multiparticulate form of the formulation of the invention makes it possible to obtain a uniform and reproducible release profile.

[0012] In addition, the granules of the invention which each contain a layer of plant substance mounted on a neutral core may be coated with an outer layer so as to modify their properties. The outer layer comprises, for example, an enteric polymer, a polymer intended to prolong the release of the plant substance or a polymer intended to mask the taste or the odour of the plant substance.

[0013] The formulation according to the invention has the advantage of being stable during storage, of having an enhanced bioavailability, and of being able to integrate high doses of plant substance.

[0014] FR 2,721,512 describes a process for the preparation of granules by extrusion-spheronization from a polymer with absorbent or adsorbent properties. The polymer is sprayed with an aqueous-alcoholic fluid plant extract.

[0015] The synthetic or natural polymer is optionally combined with auxiliary substances, such as lactose or PVP, which make it possible to modulate the porosity of the spheroids and their rate of dissolution.

[0016] The extrusion-spheronization technique has many disadvantages: it requires the addition of a quantity of water at least equal to the quantity of excipients, the granules obtained by this technique have high moisture levels and their drying takes too long. In

addition, the process described in FR 2,721,512 uses powders.

[0017] FR 2,616,068 describes a process which consists in granulating a dry or soft plant extract with methyl cellulose or silica.

[0018] FR 2,682,874 describes a process for the preparation of an extract of active ingredient in dry form from a fluid extract, which consists in adsorbing an aqueous-alcoholic solution of the active ingredient onto porous grains of cellulose or silica. The grains have a particle size which is in the micron range. These grains are then adsorbed onto porous granules 0.1 to 0.5 mm in diameter, which for example consist of sugar.

[0019] FR 2,737,134 describes a process which consists in coating cores, having a diameter of less than 0.01 mm, consisting of maltisorb or of a sodium bicarbonate/citrate mixture, with a compound in powdered form and a compound in solution. The compound in solution is an essential oil and/or a concentrated fluid plant extract.

SUMMARY

[0020] The subject of the present invention is granules which overcome the disadvantages of the prior art formulations. These granules containing at least one plant substance are characterized in that they each comprise a neutral core having a particle size of between 200 and 1600 μm coated with a layer containing the plant substance combined with a

pharmaceutically acceptable excipient.

[0021] The plant substance may be derived from plants chosen from garlic, Echinacea, Ginkgo biloba, ginseng, Harpagophytum, kava, St.-John's-wort, green tea, valerian, Missouri grape, artichoke, hawthorn, burdock, birch, alder buckthorn, blackcurrant, blessed thistle, Fucus, Hamamelis, horse chestnut, balm, Orthosiphon, passion flower, dandelion, horsetail, meadowsweet, sage, spirulina and mixtures thereof.

[0022] The neutral core consists of a substance chosen from sugar, starch, mannitol, sorbitol, xylitol, cellulose, talc and mixtures thereof.

[0023] The neutral cores may also consist of a starch/sucrose core in 20/80 mass ratios which is coated with 80% by weight of starch. In such neutral cores, the proportion by mass of sugar is advantageously less than 20%.

[0024] The layer containing the plant substance may contain a binder. A sugar such as sucrose, polyvinylpyrrolidone, lac gum or hydroxypropylmethyl-cellulose is advantageously used as binder.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0025] The granules according to the invention may consist of a neutral core coated with a layer containing the plant substance, itself coated with an outer layer intended to mask the taste and/or the odour of the plant substance, to delay its release or to control its release.

[0026] When the outer layer is intended to control the release of the plant substance, it advantageously contains lac gum, PVP, a copolymer of methacrylic acid (Eudragit®) or of Aquacoat® with a plasticizer.

[0027] As polymer intended to mask the taste and/or the odour of the plant substance, a copolymer of methacrylic acid (Eudragit NE 30D® or Eudragit E 100®) or hydroxypropylmethylcellulose (Pharmacoat®) may be used.

[0028] It is also possible to use, as enteric polymer, lac gum by spraying an alcoholic solution containing 10% by weight of lac gum. At higher concentrations, between 20 and 40%, lac gum fulfils the function of a delayed-release polymer.

[0029] In the granules, the content of plant substance is between 0.1 mg/g and 750 mg/g.

[0030] The present invention relates in particular to garlic granules with masked odour and taste, Ginkgo biloba granules, one daily dose, prolonged-release ginseng granules, enteric Harpagophytum granules, prolonged-release green tea granules, prolonged-release Orthosiphon granules, valerian granules with masked taste and odour and prolonged-release St.-John's-wort granules.

[0031] The present invention also relates to a process for the preparation of the granules described above.

[0032] The process according to the invention allows better

reproducibility of the proportion; it also makes it possible to formulate the plant substance from a dry, soft or fluid extract.

[0033] The granules according to the invention may contain several plant substances used in the form, independently of each other, of a fluid, dry or soft extract.

[0034] According to the definition given in the pharmacopoeia, plant extracts are concentrated preparations which are liquid, solid or of intermediate consistency, generally obtained from dried plant raw materials. For some preparations, the materials to be extracted may undergo a preliminary treatment (such as inactivation of enzymes, grinding or defatting).

[0035] Fluid extracts are liquid preparations of which, in general, a portion by mass or by volume corresponds to a portion by mass of dried raw material. These preparations are adjusted, if necessary, so as to meet the requirements of content of solvents, of constituents or of dry residue.

[0036] Soft extracts are preparations having an intermediate consistency between fluid extracts and dry extracts. Soft extracts are prepared by partial evaporation of the solvent which served for their preparation. Only ethanol at an appropriate titre or water are used. Soft extracts have in general a dry residue which is not less than 70 percent m/m. They may contain appropriate antimicrobial preservatives.

[0037] Dry extracts are solid preparations obtained by evaporation of the solvent which served for their production. Dry extracts have in general a dry residue which is not less than 95 percent m/m. Appropriate inert substances may be added.

[0038] According to the process of the invention, the granules are obtained by powder-coating when the plant substance is in the form of a dry extract.

[0039] Powder-coating is advantageously carried out by alternately spraying an alcoholic or aqueous-alcoholic solution of a binder, and the dry extract.

[0040] The granules are obtained by coating in solution when the plant substance is in the form of a soft or fluid extract.

[0041] In the case of a fluid extract, the active layer may be coated with a layer obtained by spraying a solution of a binder. The fluid extract preferably contains about 30 to 40% alcohol.

[0042] The process according to the invention advantageously makes it possible to limit the quantity of organic solvent used. During the process of the invention, 5 to 25% by weight of organic solvents are used.

[0043] The size of the granules used will be chosen as a function of the type of extract used and as a function of the desired proportion.

[0044] The size of the Neutres is between 950 and 1400 μm, when the plant extract is dry.

[0045] The size of the Neutres is between 900 and 1250 μm, when the plant extract is soft or fluid.

[0046] The percentage by mass of extract for the fluid extract used in the process of the invention is advantageously between 15 and 25% relative to the weight of the granules.

[0047] The percentage by mass of extract for a dry extract may be as high as 75% relative to the weight of the granules; it is preferably between 35 and 55%.

[0048] The granules according to the invention are prepared according to coating techniques known in the art, preferably in a pan or in a fluidized air bed.

[0049] The invention is illustrated without any limitation by the following examples.

Example 1

[0050] Green tea granules are prepared according to the following sequence of steps in a conventional pan. The green tea is in the form of a dry extract.

	QUANTITY (KG)
Neutres	32.5 - 33.5
Coating	
Dry extract of green tea	40.5 - 41.5
PVP at 20% in alcohol	14- 20
Precoating	
PVP at 20% in alcohol	4
Talc	1.6
Lubrication	
Talc	0.1

[0051] The Neutres used have a particle size of between 0.800 and 1.000 mm.

[0052] The green tea coating step may be carried out in a single stage or in several stages by alternately spraying the plant extract and a solution of polyvinylpyrrolidone (PVP K30®) at 20% in ethanol.

[0053] During the coating, precoating and lubricating steps, the granules are sieved at 1.0 - 1.18 mm, 1.18 - 1.25 mm and 1.18 - 1.25 mm, respectively, and then dried for 8 hours, respectively at room temperature and 30°C.

[0054] Granules of the following formula are obtained:

	Percentage by mass
Dry extract of green tea	49.9 - 52.3
Neutres	40.0 - 42.2
PVP K30®	4.5 - 6.7
Talc	2 - 2.2

[0055] Their water content is of the order of 0.7 - 1.5% by mass.

Example 2

RAW MATERIALS	**PERCENTAGE BY MASS**
Neutres	39.9
Dry extract of Harpagophytum	35.4
PVP K30	2.6
BDLG*	2.2
Alcohol 95%	19.4
Talc	0.5

*BDLG: Bleached dewaxed lac gum.

[0056] The Neutres have a particle size of between 800 and 1000 microns.

[0057] The Neutres and the plant extract are sprayed with an alcoholic solution of polyvinylpyrrolidone. The granules are sieved and dried. During a second step, a layer of lac gum is applied still using an alcohol solution of polyvinylpyrrolidone.

[0058] The granules are again sieved and dried.

[0059] Finally, the granules are lubricated with talc.

Example 3

[0060] The granules having the following composition are prepared:

RAW MATERIALS	PERCENTAGE BY MASS
Fluid extract of Harpagophyturn	18.5
Neutres	67.4
Fine crystalline sucrose	4.1
Purified water	4.1
Alcohol	5.2
Talc	0.7

according to the process described below.

[0061] The Neutres are introduced into the tank and the fluid extract is sprayed in fractions. The granules are sized by sieving and then dried under an air bed. A 33% sucrose solution in an ethanol/water mixture is then applied. The granules are again sieved and dried, and then lubricated with talc.

Example 4

RAW MATERIALS	PERCENTAGE BY MASS
Neutres	41.9
Dry extract of Ginkgo biloba	30.4
PVP K30®	5.5
Alcohol 95%	21.9
Talc	0.3

Example 5

RAW MATERIALS	PERCENTAGE BY MASS
Fluid extract of Ginkgo biloba	19.2
Neutres	61.5
PVP K30®	3.0
Alcohol 95%	12.3
Talc	4.0

[0062] The Neutres are introduced into the tank and the fluid extract is sprayed in fractions. The granules are sized by sieving and then dried under an air bed. A solution of polyvinylpyrrolidone in alcohol is then applied. The granules are again sieved and dried, and then lubricated with talc.

pics dans le chromatogramme obtenu en utilisant le procédé dit « de normalisation ». La teneur en substances apparentées n'est pas supérieure à 2,0 pour cent.

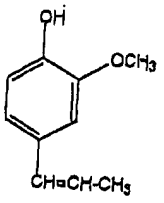
Hydrocarbures. Dans un tube à essai bouché, dissolvez 1 ml d'eugénol dans 5 ml de *solution diluée d'hydroxyde de sodium R* et ajoutez 30 ml d'*eau R*. Examinée immédiatement, la solution est jaune et limpide *(2.2.1)*. La solution se trouble au contact de l'air.

Cendres sulfuriques *(2.4.14)*. Déterminé sur 1,0 g d'eugénol, le taux des cendres sulfuriques n'est pas supérieur à 0,1 pour cent.

CONSERVATION

En récipient bien rempli et bien fermé, à l'abri de la lumière.

IMPURETÉS



A. 2-méthoxy-4-(prop-1-ényl)phénol (isoeugénol).

1997, 0765

EXTRAITS

Extracta

DÉFINITION

Les extraits sont des préparations concentrées, liquides, solides ou de consistance intermédiaire, généralement obtenues à partir de matières premières végétales ou animales séchées. Pour certaines préparations, les matières à extraire peuvent subir un traitement préalable (tel que l'inactivation d'enzymes, le broyage ou le dégraissage).

Les extraits sont préparés par macération, percolation ou par d'autres procédés appropriés et validés, en utilisant de l'éthanol ou un autre solvant approprié. Après extraction, les matières indésirables sont éliminées si nécessaire.

PRODUCTION

Production par percolation. Réduisez, si nécessaire, la drogue en morceaux de taille appropriée. Mélangez uniformément avec une partie du solvant d'extraction prescrit et laissez reposer pendant un temps approprié. Introduisez le mélange dans un percolateur et laissez le percolat s'égoutter lentement en veillant à ce que la drogue soit toujours couverte par le restant du solvant d'extraction. Le marc peut être pressé et le liquide exprimé réuni avec le percolat.

Production par macération. Sauf indication contraire, réduisez la drogue en morceaux de taille appropriée, mélangez uniformément avec le solvant d'extraction prescrit et laissez reposer le mélange dans un récipient fermé, pendant un temps approprié. La drogue épuisée est séparée du liquide extractif et, le cas échéant, pressée. Dans ce cas, les 2 liquides obtenus sont réunis.

La concentration à la consistance souhaitée est réalisée par des procédés appropriés, généralement sous pression réduite et à une température à laquelle l'altération des constituants est minime. Les solvants résiduels dans l'extrait ne dépassent pas les limites prescrites.

La teneur en constituants des extraits titrés est ajustée au moyen de substances inertes appropriées ou au moyen d'un autre extrait obtenu à partir de la matière végétale ou animale utilisée pour la préparation.

Extraits fluides

DÉFINITION

Les extraits fluides sont des préparations liquides dont, en général, une partie en masse ou en volume correspond à une partie en masse de matière première séchée. Ces préparations sont ajustées, si nécessaire, de façon à répondre aux exigences de la teneur en solvants, en constituants ou en résidu sec.

Les extraits fluides peuvent être préparés par les méthodes décrites plus haut en utilisant seulement de l'éthanol de titre approprié ou de l'eau ou par dissolution d'un extrait sec ou mou dans un de ces mêmes solvants et, si nécessaire, filtrés ; quel que soit leur mode de préparation, les extraits obtenus doivent avoir une composition comparable. Au repos, les extraits peuvent présenter un léger dépôt qui est acceptable à condition que la composition n'en soit pas modifiée de manière significative.

Les extraits fluides peuvent contenir des conservateurs antimicrobiens appropriés.

ESSAI

Densité relative *(2.2.5)*. Le cas échéant, l'extrait fluide satisfait aux limites prescrites dans la monographie.

Teneur en éthanol *(2.9.10)*. Pour les extraits fluides alcooliques, effectuez la détermination de la teneur en éthanol. La teneur en éthanol correspond à celle prescrite.

Méthanol et 2-propanol *(2.9.11)*. Sauf indication contraire, les extraits fluides alcooliques ne contiennent pas plus de 0,05 pour cent *V/V* de méthanol ni plus de 0,05 pour cent *V/V* de 2-propanol.

Résidu sec. Le cas échéant, l'extrait fluide satisfait aux limites prescrites dans la monographie. Dans une capsule à fond plat d'un diamètre de 50 mm environ et d'une hauteur de

30 mm environ, pesez rapidement 2,00 g ou introduisez 2,0 ml d'extrait. Evaporez à siccité au bain-marie et desséchez à l'étuve à 100-105 °C pendant 3 h. Laissez refroidir au dessiccateur, sur du *pentoxyde de diphosphore R*, puis pesez. Exprimez le résultat en pour cent *m/m* ou en grammes par litre.

CONSERVATION

En récipient bien fermé, à l'abri de la lumière.

ÉTIQUETAGE

L'étiquette indique :

- la drogue végétale ou animale utilisée,
- dans les cas appropriés, qu'une matière fraîche végétale ou animale a été utilisée,
- le nom et la teneur en éthanol en pour cent *V/V* du solvant utilisé pour la préparation,
- dans les cas appropriés, la teneur en éthanol en pour cent *V/V* dans l'extrait final,
- la teneur en principe actif ou le rapport entre la matière première et l'extrait fluide final,
- le nom et la concentration du conservateur antimicrobien éventuellement ajouté.

Extraits mous ou fermes

DÉFINITION

Les extraits mous ou fermes sont des préparations de consistance intermédiaire entre les extraits fluides et les extraits secs. Les extraits mous ou fermes sont préparés par évaporation partielle du solvant ayant servi à leur préparation. Seuls l'éthanol de titre approprié ou l'eau sont utilisés. Les extraits mous ou fermes ont en général un résidu sec qui n'est pas inférieur à 70 pour cent *m/m*. Ils peuvent contenir des conservateurs antimicrobiens appropriés.

ESSAI

Résidu sec. Le cas échéant, l'extrait satisfait aux limites prescrites dans la monographie. Dans une capsule à fond plat d'un diamètre de 50 mm environ et d'une hauteur de 30 mm environ, pesez rapidement 2,00 g d'extrait. Evaporez à siccité au bain-marie et desséchez à l'étuve à 100-105 °C pendant 3 h. Laissez refroidir au dessiccateur sur du *pentoxyde de diphosphore R*, puis pesez. Exprimez le résultat en pour cent *m/m*.

CONSERVATION

En récipient bien fermé, à l'abri de la lumière.

ÉTIQUETAGE

L'étiquette indique :

- la drogue végétale ou animale utilisée,
- dans les cas appropriés, qu'une matière fraîche végétale ou animale a été utilisée,
- le nom et la teneur en éthanol en pour cent *V/V* du solvant utilisé pour la préparation,
- la teneur en principe actif ou le rapport entre la matière première et l'extrait final,
- le nom et la concentration du conservateur antimicrobien éventuellement ajouté.

Extraits secs

DÉFINITION

Les extraits secs sont des préparations solides, obtenues par évaporation du solvant ayant servi à leur production. Les extraits secs ont en général un résidu sec qui n'est pas inférieur à 95 pour cent *m/m*. Des substances inertes appropriées peuvent être ajoutées.

La teneur définie en constituants des extraits secs titrés est ajustée au moyen de substances inertes appropriées ou au moyen d'un autre extrait sec de la matière végétale ou animale utilisée pour la préparation.

Dans les cas appropriés, la monographie spécifique prescrit un essai limite du solvant utilisé pour l'extraction.

ESSAI

Perte à la dessiccation (*2.2.32*). Le cas échéant, l'extrait satisfait aux limites prescrites dans la monographie. Dans une capsule à fond plat d'un diamètre de 50 mm environ et d'une hauteur de 30 mm environ, pesez rapidement 0,50 g d'extrait sec finement pulvérisé. Desséchez à l'étuve à 100-105 °C pendant 3 h. Laissez refroidir au dessiccateur, sur du *pentoxyde de diphosphore R*, puis pesez. Exprimez le résultat en pour cent *m/m*.

CONSERVATION

En récipient étanche, à l'abri de la lumière.

ÉTIQUETAGE

L'étiquette indique :

- le nom et la quantité de la substance inerte éventuellement utilisée,
- la drogue végétale ou animale utilisée,
- dans les cas appropriés, qu'une matière fraîche végétale ou animale a été utilisée,
- le nom et la teneur en éthanol en pour cent *V/V* du solvant utilisé pour la préparation,
- la teneur en principe actif ou le rapport entre la matière première et l'extrait final.

solutions with a pH within physiological limits.

Ear washes intended for application to injured parts or prior to a surgical operation are sterile.

TESTS

Deliverable mass or volume *(2.9.28)*. Ear washes supplied in single-dose containers comply with the test.

Ear Tampons

DEFINITION

Ear tampons are intended to be inserted into the external auditory meatus. They comply with the requirements of the monograph on *Medicated tampons (1155)*.

Ph Eur

Ear Preparations of the British Pharmacopoeia

In addition to the above requirements of the European Pharmacopoeia, the following statements apply to those ear drops that are the subject of an individual monograph in the British Pharmacopoeia.

EAR DROPS

Storage Ear Drops are supplied in containers of glass or suitable plastic that are fitted with an integral dropper or with a screw cap of suitable materials incorporating a dropper and rubber or plastic teat. Alternatively, such a cap assembly is supplied separately.

Labelling The label states (1) the names and concentrations of the active ingredients; (2) that the Ear Drops are intended for external use only; (3) the date after which the Ear Drops are not intended to be used; (4) the conditions under which the Ear Drops should be stored.

The following ear drops are the subject of an individual monograph in the British Pharmacopoeia.

Almond Oil Ear Drops
Aluminium Acetate Ear Drops
Chloramphenicol Ear Drops
Choline Salicylate Ear Drops
Hydrocortisone Acetate and Neomycin Ear Drops
Olive Oil Ear Drops
Sodium Bicarbonate Ear Drops

EXTRACTS

Extracts comply with the requirements of the 3rd edition of the European Pharmacopoeia (0765). These requirements are reproduced after the heading 'Definition' below.

Ph Eur

DEFINITION

Extracts are concentrated preparations of liquid, solid or intermediate consistency, usually obtained from dried vegetable or animal matter. For some preparations, the matter to be extracted may undergo a preliminary treatment, for example, inactivation of enzymes, grinding or defatting.

Extracts are prepared by maceration, percolation or other suitable, validated methods using ethanol or another suitable solvent. After extraction, unwanted matter is removed, if necessary.

PRODUCTION

Production by percolation If necessary, reduce the matter to be extracted to pieces of suitable size. Mix thoroughly with a portion of the prescribed extraction solvent and allow to stand for an appropriate time. Transfer to a percolator and allow the percolate to flow slowly making sure that the matter to be extracted is always covered with the remaining extraction solvent. The residue may be pressed out and the expressed fluid combined with the percolate.

Production by maceration Unless otherwise prescribed, reduce the matter to be extracted to pieces of suitable size, mix thoroughly with the prescribed extraction solvent and allow to stand in a closed container for an appropriate time. The residue is separated from the extraction solvent, and if necessary, pressed out. In the latter case, the two liquids obtained are combined.

Concentration to the intended consistency is carried out using suitable methods, generally under reduced pressure and at a temperature at which deterioration of the constituents is at a minimum. The residual solvents in the extract do not exceed the prescribed limits.

Standardised extracts are adjusted to the defined content of constituents using suitable inert materials or using another extract of the vegetable or animal matter used for the preparation.

Liquid Extracts

DEFINITION

Liquid extracts are fluid preparations of which, in general, one part by mass or volume is equivalent to one part by mass of the original dried drug. These preparations are adjusted, if necessary, so that they satisfy the requirements for content of solvent, for constituents or for dry residue.

Liquid extracts may be prepared by the methods described above using only ethanol of suitable concentration or water or by dissolving a soft or dry extract in one of these solvents and, if necessary, filtering; whatever their method of preparation, the extracts obtained have a comparable composition. A slight sediment may form on standing and that is acceptable as long as the composition is not changed significantly.

Liquid extracts may contain suitable antimicrobial preservatives.

TESTS

Relative density *(2.2.5)*. Where applicable, the liquid extract complies with the limits prescribed in the monograph.

Ethanol content *(2.9.10)*. For alcoholic liquid extracts, carry out the determination of ethanol content. The ethanol content complies with that prescribed.

Methanol and 2-propanol *(2.9.11)*. For alcoholic liquid extracts, not more than 0.05 per cent *V/V* of methanol and not more than 0.05 per cent *V/V* of 2-propanol, unless otherwise prescribed.

Dry residue Where applicable, the liquid extract complies with the limits prescribed in the monograph. In a

Correspondence between Ph Eur general methods and Appendices of the British Pharmacopoeia is shown on page A9

flat-bottomed dish about 50 mm in diameter and about 30 mm in height, introduce rapidly 2.00 g or 2.0 ml of the extract to be examined. Evaporate to dryness on a water-bath and dry in an oven at 100°C to 105°C for 3 h. Allow to cool in a desiccator over *diphosphorus pentoxide R* and weigh. Calculate the result as a mass percentage or in grams per litre.

STORAGE

Store in a well-closed container, protected from light.

LABELLING

The label states:
— the vegetable or animal matter used,
— where applicable, that fresh vegetable or animal matter was used,
— the name and the ethanol content in per cent *V/V* of the solvent used for the preparation,
— where applicable, the ethanol content in per cent *V/V* in the final extract,
— the content of active principle and/or the ratio of starting material to final liquid extract,
— the name and concentration of any added antimicrobial preservative.

Soft Extracts

DEFINITION

Soft extracts are preparations of an intermediate consistency, between liquid and dry extracts. They are obtained by partial evaporation of the solvent used for preparation. Only ethanol of suitable concentration or water is used. Soft extracts generally have a dry residue of not less than 70 per cent by mass. They may contain suitable antimicrobial preservatives.

TESTS

Dry residue Where applicable, the soft extract complies with the limits prescribed in the monograph. In a flat-bottomed dish about 50 mm in diameter and about 30 mm in height, weigh rapidly 2.00 g of the extract to be examined. Heat to dryness on a water-bath and dry in an oven at 100°C to 105°C for 3 h. Allow to cool in a desiccator over *diphosphorus pentoxide R* and weigh. Calculate the result as a mass percentage.

STORAGE

Store in a well-closed container, protected from light.

LABELLING

The label states:
— the vegetable or animal matter used,
— where applicable, that fresh vegetable or animal matter was used,
— the name and the ethanol content in per cent *V/V* of the solvent used for the preparation,
— the content of active principle and/or the ratio of starting material to final soft extract,
— the name and concentration of any added antimicrobial preservative.

Dry Extracts

DEFINITION

Dry extracts are solid preparations obtained by evaporation of the solvent used for their production. Dry extracts generally have a dry residue of not less than 95 per cent by mass. Suitable inert materials may be added.

Standardised dry extracts are adjusted to the defined content of constituents, using suitable inert materials or a dry extract of the vegetable or animal matter used for the preparation.

Where applicable, the monograph on a dry extract prescribes a limit test for the solvent used for extraction.

TESTS

Loss on drying (*2.2.32*). Where applicable, the dry extract complies with the limits prescribed in the monograph. In a flat-bottomed dish about 50 mm in diameter and about 30 mm in height, weigh rapidly 0.50 g of the extract to be examined, finely powdered. Dry in an oven at 100°C to 105°C for 3 h. Allow to cool in a desiccator over *diphosphorus pentoxide R* and weigh. Calculate the result as a mass percentage.

STORAGE

Store in an airtight container, protected from light.

LABELLING

The label states:
— the name and amount of any inert material used,
— the vegetable or animal matter used,
— where applicable, that fresh vegetable or animal matter was used,
— the name and the ethanol content in per cent *V/V* of the solvent used for the preparation,
— the content of active principle and/or the ratio of starting material to final dry extract.

Ph Eur

Extracts of the British Pharmacopoeia

The following extracts are the subject of an individual monograph in the British Pharmacopoeia. Those distinguished by the symbol '☆' in the list below are monographs of the European Pharmacopoeia.

Aloes Dry Extract, Standardised ☆
Belladonna Leaf Dry Extract, Standardised ☆
Cascara Dry Extract
Frangula Bark Dry Extract, Standardised ☆
Ipecacuanha Liquid Extract
Liquorice Ethanolic Liquid Extract, Stanardised ☆
Liquorice Liquid Extract
Quillaia Liquid Extract
Senna Leaf Dry Extract, Standardised ☆
Senna Liquid Extract
Squill Liquid Extract

Correspondence between Ph Eur general methods and Appendices of the British Pharmacopoeia is shown on page A9